MEFOXIN - cefoxitin sodium injection, solution
Bioniche Pharma USA LLC

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MEFOXIN[1] and other antibacterial drugs, MEFOXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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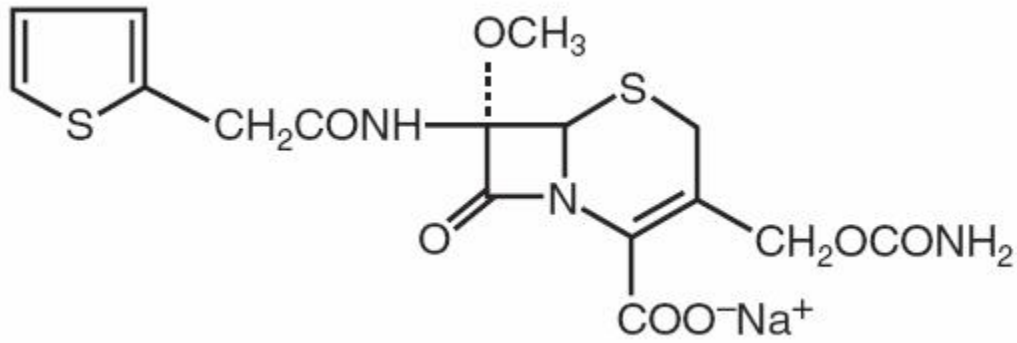
Mefoxin is a registered trademark of Bioniche Teoranta

DESCRIPTION

Cefoxitin sodium is a semi-synthetic, broad-spectrum cepha antibiotic for intravenous administration. It is derived from cephamycin C, which is produced by *Streptomyces lactamdurans.* Its chemical name is sodium (6R,7S)-3-(hydroxymethyl)-7-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate carbamate (ester). The empirical formula is $C_{16}H_{16}N_3NaO_7S_2$, and the molecular weight is 449.44. The structural formula is:



Cefoxitin sodium contains approximately 53.8 mg (2.3 milliequivalents) of sodium per gram of cefoxitin activity.
Premixed Intravenous Solution MEFOXIN (Cefoxitin Injection) is supplied as a sterile, nonpyrogenic, frozen iso-osmotic solution of cefoxitin sodium. Each 50 mL contains Cefoxitin Sodium, USP equivalent to either 1 gram or 2 grams cefoxitin. Dextrose Hydrous, USP has been added to the above dosages to adjust osmolality (approximately 2 grams and 1.1 grams to 1 gram and 2 gram dosages, respectively). The pH is adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. The pH is approximately 6.5. After thawing, the solution is intended for intravenous use only. Solutions of MEFOXIN range from colorless to light amber.
The plastic container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Clinical Pharmacology

Following an intravenous dose of 1 gram of cefoxitin, serum concentrations were 110 mcg/mL at 5 minutes, declining to less than 1 mcg/mL at 4 hours. The half-life after an intravenous dose is 41 to 59 minutes. Approximately 85 percent of cefoxitin is excreted unchanged by the kidneys over a 6-hour period, resulting in high urinary concentrations. Probenecid slows tubular excretion and produces higher serum levels and increases the duration of measurable serum concentrations.
Cefoxitin passes into pleural and joint fluids and is detectable in antibacterial concentrations in bile.
In a published study of geriatric patients ranging in age from 64 to 88 years with normal renal function for their age (creatinine clearance ranging from 31.5 to 174.0 mL/min), the half-life for cefoxitin ranged from 51 to 90 minutes, resulting in higher plasma concentrations than in younger adults. These changes were attributed to decreased renal function associated with the aging process.

Microbiology

The bactericidal action of cefoxitin results from inhibition of cell wall synthesis. Cefoxitin has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. The methoxy group in the 7α position provides cefoxitin with a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative bacteria.
Cefoxitin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Staphylococcus aureus[2] (including penicillinase-producing strains)

Staphylococcus epidermidis[2]

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Most strains of enterococci, e.g., *Enterococcus faecalis*, are resistant.

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Staphylococci resistant to methicillin/oxacillin should be considered resistant to cefoxitin.

Aerobic gram-negative microorganisms
Escherichia coli

Haemophilus influenzae

Klebsiella spp. (including *K. pneumoniae*)

Morganella morganii

Neisseria gonorrhoeae (including penicillinase-producing strains)

Proteus mirabilis

Proteus vulgaris

Providencia spp. (including *Providencia rettgeri*)

Anaerobic gram-positive microorganisms
Clostridium spp.

Peptococcus niger

Peptostreptococcus spp.

Anaerobic gram-negative microorganisms
Bacteroides distasonis

Bacteroides fragilis

Bacteroides ovatus

Bacteroides thetaiotaomicron

Bacteroides spp.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefoxitin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 8 μg/mL or less for aerobic microorganisms and 16 μg/mL or less for anaerobic microorganisms against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefoxitin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms
Eikenella corrodens [non-ß-lactamase producers]

Klebsiella oxytoca

Anaerobic gram-positive microorganisms
Clostridium perfringens

Anaerobic gram-negative microorganisms
Prevotella bivia (formerly *Bacteroides bivius*)

Cefoxitin is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae.*

Susceptibility Tests

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method (1) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefoxitin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms[3,4,5] other than *Neisseria gonorrhoeae*:

MIC (μg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

3Staphylococci exhibiting resistance to methicillin/oxacillin should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.
4For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM) 1.
5For testing streptococci these interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood 1.
For testing *Neisseria gonorrhoeae*[6]:

MIC (μg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

6Interpretative criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% $CO_2$1. A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefoxitin powder should provide the following MIC values:

Microorganism		MIC (μg/mL)
Escherichia coli	ATCC 25922	1-4
Neisseria gonorrhoeae[*]	ATCC 49226	0.5-2
Staphylococcus aureus	ATCC 29213	1-4

***** Interpretative criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% $CO_2$1.

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (2) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-μg cefoxitin to test the susceptibility of microorganisms to cefoxitin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-μg cefoxitin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms [7,8,9] other than *Neisseria gonorrhoeae*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

7Staphylococci exhibiting resistance to methicillin/oxacillin should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.
8For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by disk diffusion method using Haemophilus Test Medium (HTM) 1.
9For testing streptococci these interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% $CO_2$2.

For testing *Neisseria gonorrhoeae*[10]:

Zone Diameter (mm)	Interpretation
≥ 28	Susceptible (S)
24-27	Intermediate (I)
≤ 23	Resistant (R)

10 Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% $CO_2$2.
Interpretation should be as stated above for results using dilution techniques.

Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefoxitin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-μg cefoxitin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	23-29
Neisseria gonorrhoeae[*]	ATCC 49226	33-41
Staphylococcus aureus	ATCC 25923	23-29

*****Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% $CO_2$2.

Anaerobic Techniques:
For anaerobic bacteria, the susceptibility to cefoxitin as MIC's can be determined by standardized test methods 3. The MIC values obtained should be interpreted according to the following criteria:

MIC (μg/mL)	Interpretation
≤ 16	Susceptible (S)
32	Intermediate (I)
≥ 64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard cefoxitin powder should provide the following MIC values:

Using either an Agar Dilution Method[11] or Using a Broth[12] Microdilution Method:

Microorganism		MIC (μg/mL)
Bacteroides fragilis	ATCC 25285	4-16
Bacteroides thetaiotaomicron	ATCC 29741	8-32

11Range applicable only to tests performed using either Brucella blood or Wilkins-Chalgren agar.
12Range applicable only to tests performed in the broth formulation of Wilkins-Chalgren agar 3.

INDICATIONS AND USAGE
MEFOXIN, supplied as a premixed solution in plastic containers, is intended for intravenous use only.

Treatment
MEFOXIN is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

1. **Lower respiratory tract infections,** including pneumonia and lung abscess, caused by *Streptococcus pneumoniae*, other streptococci (excluding enterococci, e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, *Haemophilus influenzae,* and *Bacteroides* species.

2. **Urinary tract infections** caused by *Escherichia coli, Klebsiella* species, *Proteus mirabilis, Morganella morganii, Proteus vulgaris* and *Providencia* species (including *P. rettgeri*).

3. **Intra-abdominal infections,** including peritonitis and intra-abdominal abscess, caused by *Escherichia coli, Klebsiella* species, *Bacteroides* species including *Bacteroides fragilis,* and *Clostridium* species.

4. **Gynecological infections,** including endometritis, pelvic cellulitis, and pelvic inflammatory disease caused by *Escherichia coli, Neisseria gonorrhoeae* (including penicillinase-producing strains), *Bacteroides* species including *B. fragilis,Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, and *Streptococcus agalactiae.* MEFOXIN, like cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when MEFOXIN is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

5. **Septicemia** caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, and *Bacteroides* species including *B. fragilis.*

6. **Bone and joint infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains).

7. **Skin and skin structure infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Escherichia coli, Proteus mirabilis, Klebsiella* species, *Bacteroides* species including *B. fragilis,Clostridium* species, *Peptococcus niger,* and *Peptostreptococcus* species.

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organisms to MEFOXIN. Therapy may be started while awaiting the results of these studies.
In randomized comparative studies, cefoxitin and cephalothin were comparably safe and effective in the management of infections caused by gram-positive cocci and gram-negative rods susceptible to the cephalosporins. MEFOXIN has a high degree of stability in the presence of bacterial beta-lactamases, both penicillinases and cephalosporinases.
Many infections caused by aerobic and anaerobic gram-negative bacteria resistant to some cephalosporins respond to MEFOXIN. Similarly, many infections caused by aerobic and anaerobic bacteria resistant to some penicillin antibiotics (ampicillin, carbenicillin, penicillin G) respond to treatment with MEFOXIN. Many infections caused by mixtures of susceptible aerobic and anaerobic bacteria respond to treatment with MEFOXIN.

Prevention
MEFOXIN is indicated for the prophylaxis of infection in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of MEFOXIN and other antibacterial drugs, MEFOXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

WARNINGS
BEFORE THERAPY WITH 'MEFOXIN' IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO 'MEFOXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.
Clostridium difficile associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including MEFOXIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General
The total daily dose should be reduced when MEFOXIN is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see DOSAGE AND ADMINISTRATION, Treatment), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.
Antibiotics (including cephalosporins) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
As with other antibiotics, prolonged use of MEFOXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
Do not use unless solution is clear and seal is intact.
Prescribing MEFOXIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be counseled that antibacterial drugs including MEFOXIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When MEFOXIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may 1) decrease the effectiveness of the immediate treatment and 2) increase the likelihood that bacteria will develop resistance and will not be treatable by MEFOXIN or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting the treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests
As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions
Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions
As with cephalothin, high concentrations of cefoxitin (>100 micrograms/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction, and produce false increases of modest degree in the levels of creatinine reported. Serum samples from patients treated with cefoxitin should not be analyzed for creatinine if withdrawn within 2 hours of drug administration. High concentrations of cefoxitin in the urine may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction, and produce false increases of modest degree in the levels reported.

A false-positive reaction for glucose in the urine may occur. This has been observed with CLINITEST[13] reagent tablets.

13
Clinitest is a trademark of Siemens Healthcare Diagnostics, Inc.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed with cefoxitin to evaluate carcinogenic or mutagenic potential. Studies in rats treated intravenously with 400 mg/kg of cefoxitin (approximately three times the maximum recommended human dose) revealed no effects on fertility or mating ability.

Pregnancy
Pregnancy Category B.
Reproduction studies performed in rats and mice at parenteral doses of approximately one to seven and one-half times the maximum recommended human dose did not reveal teratogenic or fetal toxic effects, although a slight decrease in fetal weight was observed.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

In the rabbit, cefoxitin was associated with a high incidence of abortion and maternal death. This was not considered to be a teratogenic effect but an expected consequence of the rabbit's unusual sensitivity to antibiotic-induced changes in the population of the microflora of the intestine.

Nursing Mothers
Cefoxitin is excreted in human milk in low concentrations. Caution should be exercised when MEFOXIN is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients from birth to three months of age have not yet been established. In pediatric patients three months of age and older, higher doses of cefoxitin have been associated with an increased incidence of eosinophilia and elevated SGOT.
The potential for toxic effects in pediatric patients from chemicals that may leach from the single-dose I.V. preparation in plastic has not been determined.

Geriatric Use
Of the 1,775 subjects who received cefoxitin in clinical studies, 424 (24%) were 65 and over, while 124 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY).
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

ADVERSE REACTIONS
Cefoxitin is generally well tolerated. The most common adverse reactions have been local reactions following intravenous injection. Other adverse reactions have been encountered infrequently.

Local Reactions
Thrombophlebitis has occurred with intravenous administration.

Allergic Reactions
Rash (including exfoliative dermatitis and toxic epidermal necrolysis), urticaria, flushing, pruritus, eosinophilia, fever, dyspnea, and other allergic reactions including anaphylaxis, interstitial nephritis and angioedema have been noted.

Cardiovascular
Hypotension.

Gastrointestinal
Diarrhea, including documented pseudomembranous colitis which can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Neuromuscular
Possible exacerbation of myasthenia gravis.

Blood
Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia.

Liver Function
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase; and jaundice have been reported.

Renal Function
Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of MEFOXIN in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function usually have been present.
In addition to the adverse reactions listed above which have been observed in patients treated with MEFOXIN, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:
Urticaria, erythema multiforme, Stevens-Johnson syndrome, serum sickness-like reactions, abdominal pain, colitis, renal dysfunction, toxic nephropathy, false-positive test for urinary glucose, hepatic dysfunction including cholestasis, elevated bilirubin, aplastic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, agranulocytosis, superinfection, vaginitis including vaginal candidiasis.
Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See DOSAGE AND ADMINISTRATION.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE
The acute intravenous LD_{50} in the adult female mouse and rabbit was about 8.0 g/kg and greater than 1.0 g/kg, respectively. The acute intraperitoneal LD_{50} in the adult rat was greater than 10.0 g/kg.

DOSAGE AND ADMINISTRATION
NOTE: MEFOXIN® in Galaxy[14] container is for intravenous infusion only.

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Galaxy® is a registered trademark of Baxter International Inc.

Treatment

Adults
The usual adult dosage range is 1 gram to 2 grams every six to eight hours. Dosage should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient (see Table 1 for dosage guidelines).

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefoxitin sodium has no activity against this organism.

MEFOXIN may be used in patients with reduced renal function with the following dosage adjustments:

In adults with renal insufficiency, an initial loading dose of 1 gram to 2 grams may be given. After a loading dose, the recommendations for *maintenance dosage* (Table 2) may be used as a guide.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.85 x male value

In patients undergoing hemodialysis, the loading dose of 1 to 2 grams should be given after each hemodialysis, and the maintenance dose should be given as indicated in Table 2.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Pediatric Patients
The recommended dosage in pediatric patients three months of age and older is 80 to 160 mg/kg of body weight per day divided into four to six equal doses. The higher dosages should be used for more severe or serious infections. The total daily dosage should not exceed 12 grams.

At this time no recommendation is made for pediatric patients from birth to three months of age (see PRECAUTIONS).

In pediatric patients with renal insufficiency, the dosage and frequency of dosage should be modified consistent with the recommendations for adults (see Table 2).

Prevention
Effective prophylactic use depends on the time of administration. MEFOXIN usually should be given one-half to one hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.
For prophylactic use in uncontaminated gastrointestinal surgery, vaginal hysterectomy, or abdominal hysterectomy, the following doses are recommended:

Adults:
2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours.

Pediatric Patients (3 months and older):
30 to 40 mg/kg doses may be given at the times designated above.

Cesarean section patients:
For patients undergoing cesarean section, either a single 2 gram dose administered intravenously as soon as the umbilical cord is clamped OR a 3-dose regimen consisting of 2 grams given intravenously as soon as the umbilical cord is clamped followed by 2 grams 4 and 8 hours after the initial dose is recommended. (See CLINICAL STUDIES.)

Table 1 - Guidelines for Dosage of MEFOXIN

Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, cutaneous infection	3-4 grams	1 gram every 6-8 hours IV
Moderately severe or severe infections	6-8 grams	1 gram every 4 hours *or* 2 grams every 6-8 hours IV
Infections commonly needing antibiotics in higher dosage (e.g., gas gangrene)	12 grams	2 grams every 4 hours *or* 3 grams every 6 hours IV

***** Including patients in whom bacteremia is absent or unlikely.

Table 2 - Maintenance Dosage of MEFOXIN in Adults with Reduced Renal Function

Renal Function	Creatinine Clearance (mL/min)	Dose (grams)	Frequency
Mild impairment	50-30	1-2	every 8-12 hours
Moderate impairment	29-10	1-2	every 12-24 hours
Severe impairment	9-5	0.5-1	every 12-24 hours
Essentially no function	<5	0.5-1	every 24-48 hours

Administration

This premixed solution is for intravenous use only. Premixed Intravenous Solution MEFOXIN in Galaxy® containers (PL 2040 Plastic) is to be administered either as a continuous or intermittent infusion using sterile equipment. Scalp vein-type needles are preferred for this type of infusion. It is recommended that the intravenous administration apparatus be replaced at least once every 48 hours.

The intravenous route is preferred for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

Directions for Use of Galaxy® Containers (PL 2040 Plastic)

Thaw frozen container at room temperature, 25°C (77°F), or under refrigeration, 2-8°C (36-46°F). DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.

After thawing, check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

The container should be visually inspected for particulate matter and discoloration prior to administration. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Agitate after solution has reached room temperature.

Do not use if the solution is cloudy or a precipitate has formed. If any seals or outlet ports are not intact, the container should be discarded. Solutions of MEFOXIN tend to darken depending on storage conditions; product potency, however, is not adversely affected.

Additives should not be introduced into this solution.

CAUTION: Do not use plastic containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Intravenous Administration:

1. Suspend container from eyelet support.

2. Remove plastic protector from outlet port at bottom of container.

3. Attach administration set. Refer to complete directions accompanying set.

MEFOXIN may be administered through the tubing system by which the patient may be receiving other intravenous solutions. However, during infusion of the solution containing MEFOXIN, it is advisable to temporarily discontinue administration of any other solutions at the same site.

Solutions of MEFOXIN, like those of most beta-lactam antibiotics, should not be added to aminoglycoside solutions (e.g., gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction. However, MEFOXIN and aminoglycosides may be administered separately to the same patient.

Stability

MEFOXIN, supplied as frozen, premixed, iso-osmotic solution in Galaxy® containers (PL 2040 Plastic), maintains satisfactory potency after thawing for 24 hours at a room temperature of 25°C (77°F) or 21 days under refrigeration, 2-8°C (36-46°F). After these periods, any unused solutions should be discarded.

DO NOT REFREEZE.

HOW SUPPLIED

Premixed Intravenous Solution MEFOXIN is supplied in single dose Galaxy® containers (PL 2040 Plastic) containing cefoxitin sodium as follows:

No. 2G3506 - 1 gram cefoxitin equivalent, iso-osmotic in 50 mL diluent containing approximately 2 grams dextrose hydrous USP **NDC** 67457-189-01 in boxes of 24.

No. 2G3507 - 2 grams cefoxitin equivalent, iso-osmotic in 50 mL diluent containing approximately 1.1 grams dextrose hydrous USP **NDC** 67457-216-50 in boxes of 24.

Special storage instructions

Store at or below –20°C (–4°F). [See Directions for Use of Galaxy® container (PL 2040 Plastic).]

MEFOXIN is also available in dry powder form in vials containing sterile cefoxitin sodium equivalent to either 1 gram or 2 grams of cefoxitin, and in vials for pharmacy bulk use containing sterile cefoxitin sodium equivalent to 10 grams of cefoxitin, for constitution and intravenous administration (see appropriate product circular).

CLINICAL STUDIES

A prospective, randomized, double-blind, placebo-controlled clinical trial was conducted to determine the efficacy of short-term prophylaxis with MEFOXIN in patients undergoing cesarean section who were at high risk for subsequent endometritis because of ruptured membranes. Patients were randomized to receive either three doses of placebo (n=58), a single dose of MEFOXIN (2 g) followed by two doses of placebo (n=64), or a three-dose regimen of MEFOXIN (each dose consisting of 2 g) (n=60), given intravenously, usually beginning at the time of clamping of the umbilical cord, with the second and third doses given 4 and 8 hours post-operatively. Endometritis occurred in 16/58 (27.6%) patients given placebo, 5/63 (7.9%) patients given a single dose of MEFOXIN, and 3/58 (5.2%) patients given three doses of MEFOXIN. The differences between the two groups treated with MEFOXIN and placebo with respect to endometritis were statistically significant ($p<0.01$) in favor of MEFOXIN. The differences between the one-dose and three-dose regimens of MEFOXIN were not statistically significant.

Two double-blind, randomized studies compared the efficacy of a single 2 gram intravenous dose of MEFOXIN to a single 2 gram intravenous dose of cefotetan in the prevention of surgical site-related infection (major morbidity) and non-site-related infections (minor morbidity) in patients following cesarean section. In the first study, 82/98 (83.7%) patients treated with MEFOXIN and 71/95 (74.7%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: –0.03, +0.21) was not statistically significant. In the second study, 65/75 (86.7%) patients treated with MEFOXIN and 62/76 (81.6%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: –0.08, +0.18) was not statistically significant.

In clinical trials of patients with intra-abdominal infections due to *Bacteroides fragilis* group microorganisms, eradication rates at 1 to 2 weeks post treatment for isolates were in the range of 70% to 80%. Eradication rates for individual species are listed below:

Bacteroides distasonis	7/10	(70%)
Bacteroides fragilis	26/33	(79%)
Bacteroides ovatus	10/13	(77%)
B. thetaiotaomicron	13/18	(72%)

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.

3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Fourth Edition. Approved Standard NCCLS Document M11-A4, Vol. 17, No. 22, NCCLS, Villanova, PA, December 1997.

Manufactured for:
Bioniche Pharma USA LLC, Lake Forest, IL 60045
Manufactured By:
Baxter Healthcare Corporation, Deerfield, Illinois 60015 USA
Date Prepared: 07/2008
071958032

PRINCIPAL DISPLAY PANEL - 1 GRAM BAG
BIONICHEPHARMA
MEFOXIN®
(CEFOXITIN INJECTION)
Premixed Intravenous Solution
1 g
Cefoxitin
Equivalent
GALAXY
Single Dose
Container
50 mL
Iso-osmotic

NDC 67457-189-01
Code 2G3506
Sterile Nonpyrogenic
Each 50 mL contains: Cefoxitin Sodium, USP equivalent to 1 g cefoxitin with approximately 2 g Dextrose Hydrous, USP added to adjust osmolality. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid.
USUAL DOSAGE: See package insert. Administer intravenously as directed by a physician.
CAUTIONS: Do not add supplementary medication. Must not be used in series connections. Check for minute leaks by squeezing thawed bag firmly. Discard bag if leaks are found or solution is not clear.
Rx only
Store at or below -20°C (-4°F). Thaw at room temperature, 25°C (77°F), or under refrigeration, 2-8°C (36-46°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution is stable for 21 days under refrigeration or 24 hours at room temperature. **Do not refreeze.**

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by **Baxter Healthcare Corporation**, Deerfield, IL 60015 USA
PL 2040 Plastic
07-34-56-300
07-34-56-300

PRINCIPAL DISPLAY PANEL - 2 GRAM BAG
BIONICHEPHARMA
MEFOXIN®
(CEFOXITIN INJECTION)
Premixed Intravenous Solution
2 g
Cefoxitin
Equivalent
GALAXY
Single Dose
Container
50 mL
Iso-osmotic
NDC 67457-189-02
Code 2G3507
Sterile Nonpyrogenic
Each 50 mL contains: Cefoxitin Sodium, USP equivalent to 2 g cefoxitin with approximately 1.1 g Dextrose Hydrous, USP added to adjust osmolality. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid.
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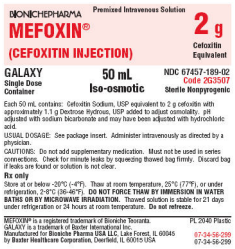
PL 2040 Plastic
07-34-56-299
07-34-56-299


BIONICHEPHARMA
Premixed Intravenous Solution
MEFOXIN®
(CEFOXITIN INJECTION)
2 g
Cefoxitin Equivalent
GALAXY
Single Dose Container
50 mL
Iso-osmotic
NDC 67457-189-02
Code 2G3507
Sterile Nonpyrogenic
Each 50 mL contains: Cefoxitin Sodium, USP equivalent to 2 g cefoxitin with approximately 1.1 g Dextrose Hydrous, USP added to adjust osmolality. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid.
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